PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 June 2000 (13.06.00)	
International application No. PCT/US99/24879	**Applicant's or agent's file reference** D-0021.5 PCT
International filing date (day/month/year) 22 October 1999 (22.10.99)	**Priority date** (day/month/year) 23 October 1998 (23.10.98)
Applicant ZAVADA, Jan et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   11 May 2000 (11.05.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
D-0021.5 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/24879	22/10/1999	23/10/1998
International Patent Classification (IPC) or national classification and IPC C12N15/63		
Applicant BAYER CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/05/2000	16.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Julia, P Telephone No. +49 89 2399 8410

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/24879

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-4,6-25,27-74	as originally filed			
5,26	as received on	03/01/2001	with letter of	02/01/2001

Claims, No.:

12-27,31-45,47	as received on	03/01/2001	with letter of	02/01/2001

Drawings, sheets:

1/13-13/13	as originally filed

Sequence listing part of the description, pages:

1-61, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☒ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence

listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:
☒ the claims, Nos.: 1-11, 28-30, 46
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 31-45, 47.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 31-32, 35, 45, 47
	No:	Claims 33-34, 36-44
Inventive step (IS)	Yes:	Claims 31-32, 45, 47
	No:	Claims 33-44
Industrial applicability (IA)	Yes:	Claims 31-45, 47
	No:	Claims

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Additional remarks to item I :

A "Sequence Listing" has been originally filed which comprises SEQ ID No.: 1 to SEQ ID No.: 143 (pages 1-61).

2. Additional remarks to item II :

The priority documents pertaining to the present application were not available at the time of establishing this international preliminary report (IPER). Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (23.10.98).

3. Additional remarks to item IV :

The IPEA agrees with the non-unity objection originally raised by the International Search Agency (ISA) (**Rule 13 PCT**). The following multiple (groups of) inventions have been identified :

1. **claims 1-11 or claims 31-44 :** an organic or inorganic molecule that binds specifically to a site on a MN protein and inhibits the adhesion of cells to the MN protein in vitro. In particular, a protein or polypeptide selected from the group consisting of SEQ ID Nos.: 107, 108, 109, 137 and 138.

2. **claims 12-19 :** a MN protein or MN polypeptide which prevents the formation of intercellular contacts and the adhesion of vertebrate cells to each other. A method for identifying a site on said MN protein to which vertebrate cells adhere.

3. **claims 20-23 :** a vector comprising a nucleic acid encoding the variable domains of a MN-specific antibody wherein said domains are separated by a flexible linker polypeptide.

4. **claims 24-27 :** a vector comprising a nucleic acid that encodes a cytotoxic protein operably linked to the MN gene promoter.

5. **claims 28-30 or claims 45-47 :** a repressor complex that binds to the MN gene promoter. In particular, wherein said complex comprises two proteins having molecular weights of 35 and 42 kD, respectively, and bind to the MN gene promoter sequences SEQ

ID Nos.: 115 and/or SEQ ID No.: 143.

The claims are considered to lack unity of invention (**Rule 13 PCT**) since they are directed to five separate groups of inventions not so linked as to be based on a common underlying inventive concept. Claims 1, 12, 20, 24 and 28 relate to different solutions for different technical problems. These different problems and their solutions are not interrelated from a technical point of view so as to form a single general inventive concept. The problem of the identification of organic or inorganic molecules which bind to the MN binding protein and inhibit cell adhesion to the MN protein is not necessarily linked with the problem of providing a MN protein which prevents the formation of intercellular contacts and adhesion of vertebrate cells to each other. This has also nothing to do with the problem of providing a repressor complex capable of binding the MN gene promoter. Further, the provision of a vector encoding variable domains of the known MN-antibodies M75 or MN12, which variable domains are separated by a flexible linker polypeptide is technically independent from the provision of a vector comprising a nucleic acid sequence that encodes a cytotoxic protein operably linked to the MN gene promoter.

Each of the above inventions therefore constitutes a separate solution to a separate technical problem. As acknowledged on pages 1-5 of the description, the MN gene and protein were well-known in the art at the priority date of the present application. In view of this, the mere common reference to MN cannot provide such a unitary link. Thus, the different inventions or group of inventions do not belong to a **common inventive conc pt** (no common technical feature over the known prior art) and the IPEA maintains the non-unity objection originally raised by the ISA (**Rule 13 PCT**).

Upon the invitation to restrict or to pay additional fees issued by the IPEA, the Applicant elected to have the inventions of group 1 (originally filed claims 1 to 11) and of group 5 (originally filed claims 28-30) examined. The Applicant further requested to cancel claims 1 to 11, claims 28 to 30 and claim 46 maintaining claims 12-27 (not searched/nor examined), 31-45 and 47. Thus, the present IPER concerns only **claims 31 to 44** (first group of invention) and **claims 45 and 47** (fifth group of invention).

4. Additional remarks to item V :

The present application relates to the MN gene which encodes the MN protein which is

also known as tumour-associated carbonic anhydrase (CA) isoenzyme IX (MN/CA IX protein), twin p54/58N protein or MN/G250 protein (mediates attachment of vertebrate cells in cell adhesion assay) (MN cDNA SEQ ID No.: 1 Fig. 1, genomic MN SEQ ID No.: 5, Fig. 2; with an intron-exon map in Fig. 5 and Table 1, wherein putative MN signal peptide SEQ ID No.: 6, extracellular domain 38-414 SEQ ID No.: 87, transmembrane domain 415-434 SEQ ID No: 52 and intracellular domain 435-459 SEQ ID No.: 53). The (abnormal) expression of the MN gene has been shown to be associated with tumorigenicity. The present application discloses the location of two MN protein binding sites, namely (i) within the proteoglycan-like domain (SEQ ID No.: 50), particularly from aa 61-96 (SEQ ID No.: 97) (6-fold tandem repeat of 6 residues, within which resides the epitope for M75 MAb) and (ii) within the CA domain (SEQ ID No.: 51) (both proteoglycan-like and CA domains are in the extracellular domain). These disclosed binding sites on the MN protein (SEQ ID No.: 10, 97-106) are the ones to which vertebrate (mammalian, preneoplastic or neoplastic) cells bind or adhere in a cell adhesion assay and which are used to identify (therapeutic) peptides blocking this interaction (SEQ ID No: 107, 108, 109, 137 and 138) (example 3). The application further refers to the inhibition of growth of vertebrate (mammalian) preneoplastic or neoplastic cells that abnormally express MN protein, in particular using a repressor complex comprising two proteins having a molecular weight of 35 and 42 kilodaltons respectively and which bind to the MN gene promoter (SEQ ID No.: 27 and Fig.6, mutational deletion analysis of minimal binding site identifies SEQ ID No.: 115 (PR4) and 143).

i) Concerning the **first** group of inventions (**claims 31-44**) :

None of the documents cited in the International Search Report (ISR) has been cited as being relevant for the novelty and/or inventiveness of the specific protein or polypeptide consisting of SEQ ID No.: 107, 108, 109, 137 and 138. In principle claims directed to these specific products are considered be novel and they are not derivable from this cited prior art in an obvious manner (Articles 33 (2) and (3) PCT). Thus, claims 31 and 32 directed specifically to the peptides of SEQ ID No.: 107, 108, 109, 137 and 138 or polypeptides or proteins comprising such peptides and fulfilling the required functional limitation, i.e. binding specifically to a site on a MN protein to which vertebrate cells adhere in a cell adhesion assay as described in example 2 (and with the ability to inhibit said adhesion), are considered to be novel and inventive (Articles 33 (2) and (3) PCT).

In respect of the method of claims 33-44, apart from the remarks made under Article 6 PCT below, the IPEA considers that it does not fulfil the requirements of Articles 33 (2) and/or (3) PCT in view of the cited documents :

a) J. Zavada et al., Int. J. Oncology 1997, Vol. 10 (4), pages 857-863 (**D1**) discloses that cells transfected with MN cDNA show morphological transformation for 4-5 weeks and later reversion. D1 identifies MN as an adhesion protein involved in cell-to-cell contact and describes a cell adhesion assay (paragraph bridging pages 858-859), wherein the MN protein is spotted on Petri dishes (protein-coated) and the adhesion of different cells is tested. D1 identifies NIH3T3, CGL1, CGL3 (abnormally expressing MN protein), HeLa and Vero cells as specifically adhering to the MN protein. For checking this specificity, the adhesion is (specifically) blocked with an excess of Mab M75 (page 861). Thus, D1 discloses a method of identifying an organic molecule (the MN-specific antibody Mab M75) that binds specifically to a site on a MN protein (proteoglycan-like domain, SEQ ID No.: 97), to which vertebrate cells (NIH3T3, CGL1, CGL3, etc...) adhere in a cell adhesion assay which also comprises the further steps of claim 33. Dependent claims 34, 37-38 ("...comprising an amino acid sequence...") do not actually characterize the claimed method but only the identified organic molecule (see below under "Additional remarks to item VIII") and claims 39-44 are anticipated by D1 too (Articles 33 (2) and (3) PCT). Moreover, in view of this disclosure, the subject matter of claim 35 does not require any further inventive skill (Article 33 (3) PCT).

b) WO95/34650 (**D2**) refers to several MN antigens of interest for isolating specific anti-MN antibodies similar to the disclosed M75 and MN12 (MN9, MN7 or their equivalents, see pages 58-61, wherein page 61 refers to epitope mapping with overlapping peptides of 20 residues). On page 31 lines 29-31 reference is made to the fact that "... the CA-like domain of MN has a structural predisposition to serve as a binding site for small soluble domains ...". These "small soluble domains" in principle fall under the scope of at least claim 31. Moreover, the IPEA considers that once the "cell adhesion assay" of D1 was known by the skilled person it would not have required any inventive contribution to either (i) substitute the MN protein for parts thereof (including the CA-like domain) and/or (ii) use these "small soluble domains" in this assay for studying their effects on the function of the MN protein. In any case, the skilled person would have achieved the subject matter of claims 33-44 in an obvious manner (Article 33 (3) PCT). D2 also refers to the possible function of the MN protein in cellular growth (page 69 lines 15-17) and more particularly in intercellular

communication or cell adhesion (page 70 lines 12-13 and page 76 lines 5-7).

A similar disclosure is found in J. Pastorek et al., Oncogene 1994, Vol. 9, pages 2877-2888 (**D3**) which discloses the cloning and characterization of the human tumour-associated MN/CA gene and the corresponding protein as well as its possible involvement in the control of cell proliferation and transformation. D3 explicitly refers to "... the capacity of CA to bind a variety of compounds ... suggests that this domain could serve as a binding site for small soluble ligands ..." (page 2885, right column).

c) R. Opavsky et al., Genomics 1996, Vol. 33, pages 480-487 (**D4**) discloses the isolation, sequence and characterization of the human tumour-associated MN/CA9 gene and the corresponding protein, including the 5'-flanking region. The document refers to the analysis of the 3.5kb upstream region (RNAse protection assays) and the sequence of the proximate 5' end of the flanking region (characterization of the putative promoter) (figure 6).

ii) Concerning the **fifth** group of inventions (**claims 45 and 47**) :

In the ISR, **D2** has been cited as being relevant for assessing the novelty and inventiveness of the claimed "repressor complex". For this subject matter, the attention of the Applicant is drawn to the sheet PCT/ISA/210 of the ISR, wherein the ISA states that "...given that the application fails to identify any repressor complex, the search concerning claim 28 has been restricted to antisense constructs as defined on pages 38-39 of the description". There is only one reference on page 29 of the description to a "repressor complex" and this reference is far away from a clear and unambiguous characterization of any "complex" (see below under "Additional remarks to item VIII").

D2 discloses the sequence of the MN gene promoter (Figure 6, SEQ ID No.: 27) and refers to the construction and cloning of a series of 5' deletion mutants of the MN putative promoter region linked to the bacterial CAT gene (Figure 8). On page 27 to page 28 reference is made to the characterization of the 5' flanking region of the MN gene and on page 29 to 30 to the characterization of the MN promoter. Pages 43 to 46 refer to the regulation of the MN expression and of the MN promoter with an explicit reference to a putative MN suppressor in chromosome 11 (page 43 lines 34-36) and to "... a putative

regulatory element ... acting via the MN promoter" (page 44 lines 35-38) (see also page 46, lines 23-26). There is no further identification of said putative regulatory element and, even if it was obvious to try to identify it, there is no indication that allows the IPEA to infer that it actually corresponds to the one claimed in the present application (claims 45 and 47). A similar disclosure is also found in document **D4** (see paragraph (c) above) (in particular reference on page 486 left-column to "... analysis of transcriptional regulation of the MN/CA9 gene...").

Figure 6 of the present application indicates that the MN promoter is actually regulated by well-known proteins such as AP2, p53, AP1, etc... There are known (cellular) proteins or factors with the MW indicated in the claims, which negatively regulate the transcription of different genes, either by directly repression of the transcription or else, if they are activators, by association with other known factors (and repression of the transcription). The CCAAT/enhancer-binding proteins (C/EBP) (a CCAAT sequence is found in positions -15 to -11 of the MN promoter in Figure 6), in particular the p42- and p35-C/EBP factors, are able to form homo- and heterodimers which regulate the transcription of different promoters including the ones having the promoter element SRE (serum response element) in a SRF (serum response factor) dependent manner (major components of three EFII DNA binding complexes which under certain conditions can repress EFII mediated transcription), p42 is also a well-known (MAPK) kinase which mediates signal transduction from the cells surface to the nucleus and through its activation by phosphorylation leads to translocation into the nucleus and phosphorylation/association/complex of certain transcription factors (possible association with AP1, AP2, etc....???), etc... However, none of these known transcription factors seems to bind to the specific SEQ ID No.: 115 (Figure 6). Thus, in the absence of a prior art clearly anticipating the claimed subject matter, the IPEA considers that the claimed subject matter of claims 45 and 47 can be acknowledged as novel and inventive (Articles 33 (2) and (3) PCT) (bearing in mind, however, the lack of a meaningful and complete characterization (see "Additional remarks to item VIII" below).

5. Additional remarks to item VIII :

The following objections are also raised under **Article 6 PCT** concerning the clarity of the claims :

i) according to PCT International Preliminary Examination Guidelines, III-4.10 the claims

must not, in respect of the technical features of the invention, rely on references to the description or drawings "except where absolutely necessary". Claim 1 relies on the reference to example 2 for defining the specific conditions of the "cell adhesion assay" but it is not clear whether said conditions are the ones used for the in vitro inhibition test (contrary to the subject matter of claim 2, wherein it is clearly required that the "testing" is performed as "the cell adhesion assay as described in Example 2").

ii) the IPEA considers that "a method of identifying an organic or an inorganic molecule that binds specifically to a site on a MN protein (with desired functional properties)" (claim 33) is actually different from "a method of identifying a site on a MN protein (with desired functional properties)" (originally filed claim 19). Whereas for the first method an essential technical feature for identifying the molecules is the "site on a MN protein" (having the desired properties), for the second method the essential technical feature is the "organic and/or inorganic molecule" (series of overlapping peptides in originally filed claim 19, SEQ ID No.: 107-109, 137, etc....) used for identifying said "MN site". Thus, apart from possible problems under Rule 70.2(c) PCT, the IPEA considers that claim 33 does not fulfil the requirements of Article 6 PCT because it does not clearly define, characterize or disclose the "essential technical feature" of the claimed method, namely the site on a MN protein, which is only characterized by the desired functional features (PCT International Preliminary Examination Guidelines, III-4.4). These MN sites are only defined and clearly characterized in claims 41 and 42. Moreover, claims 34-38 actually define products which, in principle, can be identified by the method of claim 33 but which do not characterize in any way said method.

iii) the wording "complex" is considered to be completely ambiguous (does it comprise any type of association, such as covalently bound or linked, non-covalently linked, close proximity, functional association, etc....???). There is only one reference to said "repressor complex" in the description (page 29) (page 9 refers to a "protein" and pages 39-40 to "transcription factors"). However, this reference does not clearly exclude the presence of further "components" or "elements" (proteins or polypeptides) which thus, should be seen as part of the claimed "repressor complex". The IPEA further considers that the indication of the molecular weight (MW) as the sole technical feature is not enough for clearly characterizing a protein (or proteins in this case). The MW is always an imprecise measure with an approximate value within a particular range and being highly dependent on the method (and standards) used for its determination (SDS-PAGE, gel chromatography,

Western blotting, etc...). None of these parameters have been clearly indicated in the description let alone in the wording of the claims.

iv) in view of the new set of claim and the subject matter actually searched and examined, the IPEA notes the presence of several inconsistencies between the description (reference to particular embodiments of the invention) and said set of claims (see also "Additional remarks to item VII" above and PCT International Preliminary Examination Guidelines, III-4.3).

salivary glands [Parkkila et al., Gut, 35: 646-650 (1994); Fleming et al., J. Clin. Invest., 96: 2907-2913 (1995); Parkkila et al., Hepatology, 24: 104 (1996)].

MN/CA IX has a number of properties that distinguish it from other known CA isoenzymes and evince its relevance to oncogenesis. Those properties include its density dependent expression in cell culture (e.g., HeLa cells), its correlation with the tumorigenic phenotype of somatic cell hybrids between HeLa and normal human fibroblasts, its close association with several human carcinomas and its absence from corresponding normal tissues [e.g., Zavada et al., Int. J. Cancer, 54: 268-274 (1993); Pastorekova et al., Virology, 187: 620-626 (1992); Liao et al., Am. J. Pathol., 145: 598-609 (1994); Pastorek et al., Oncogene, 9: 2788-2888 (1994); Cote, Women's Health Weekly: News Section, p. 7 (March 30, 1998); Liao et al., Cancer Res., 57: 2827 (1997); Vermylen et al., "Expression of the MN antigen as a biomarker of lung carcinoma and associated precancerous conditions," Proceedings AACR, 39: 334 (1998); McKiernan et al., Cancer Res., 57: 2362 (1997); and Turner et al., Hum. Pathol., 28(6): 740 (1997)]. In addition, the *in vitro* transformation potential of MN/CA IX cDNA has been demonstrated in NIH 3T3 fibroblasts [Pastorek et al., id.].

The MN protein has also been identified with the G250 antigen. Uemura et al., "Expression of Tumor-Associated Antigen MN/G250 in Urologic Carcinoma: Potential Therapeutic Target," J. Urol., 154 (4 Suppl.): 377 (Abstract 1475; 1997) states: "Sequence analysis and database searching revealed that G250 antigen is identical to MN, a human tumor-associated antigen identified in cervical carcinoma (Pastorek et al., 1994)."

SUMMARY OF THE INVENTION

Identified herein is the location of the MN protein binding site. Of particular importance is the region within the proteoglycan-like domain, aa 61-96 (SEQ ID NO: 97) which contains a 6-fold tandem repeat of 6 amino acids, and within which the epitope for the M75 MAb resides in at least two copies, and within which the MN binding sit is considered to be located. An alternative MN binding site may be located in the CA domain.

TABLE 1

Exon-Intron Structure of the Human MN Gene

Exon	Size	Genomic Position**	SEQ ID NO	5'splice acceptor	SEQ ID NO
1	445	*3507-3951	28	AGAAG gtaagt	67
2	30	5126-5155	29	TGGAG gtgaga	68
3	171	5349-5519	30	CAGTC gtgagg	69
4	143	5651-5793	31	CCGAG gtgagc	70
5	93	5883-5975	32	TGGAG gtacca	71
6	67	7376-7442	33	GGAAG gtcagt	72
7	158	8777-8934	34	AGCAG gtgggc	73
8	145	9447-9591	35	GCCAG gtacag	74
9	27	9706-9732	36	TGCTG gtgagt	75
10	82	10350-70431	37	CACAG gtatta	76
11	191	10562-10752	38	ATAAT end	

Intron	Size	Genomic Position **	SEQ ID NO	3'splice acceptor	SEQ ID NO
1	1174	3952-5125	39	atacag GGGAT	77
2	193	5156-5348	40	ccccag GCGAC	78
3	131	5520-5650	41	acgcag TGCAA	79
4	89	5794-5882	42	tttcag ATCCA	80
5	1400	5976-7375	43	ccccag GAGGG	81
6	1334	7443-8776	44	tcacag GCTCA	82
7	512	8935-9446	45	ccctag CTCCA	83
8	114	9592-9705	46	ctccag TCCAG	84
9	617	9733-10349	47	tcgcag GTGACA	85
10	130	10432-10561	48	acacag AAGGG	86

** positions are related to nt numbering in whole genomic sequence including the 5' flanking region [Figure 2A-F]

* number corresponds to transcription initiation site determined below by RNase protection assay

CLAIMS

1. An organic or inorganic molecule that binds specifically to a site on
CANCELLED MN protein to which vertebrate cells adhere in a cell adhesion assay, wherein said
molecule when tested in vitro inhibits the adhesion of cells to MN protein.

2. The organic or inorganic molecule of Claim 1 wherein said molecule,
CANCELLED when in contact with a vertebrate preneoplastic or neoplastic cell that abnormally
expresses MN protein, inhibits the growth of said cell.

CANCELLED ~~3. The molecule of Claims 1 and 2 which is organic.~~

CANCELLED ~~4. The molecule of Claim 3 which is a protein or a polypeptide.~~

5. The molecule of Claim 4 wherein said protein or polypeptide
CANCELLED comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:
~~107, 108,~~ 109, 137 and 138.

6. The molecule of Claim 4 wherein said polypeptide is selected from the
CANCELLED group consisting of SEQ ID NOS: 107, 108, 109, 137 and 138.

7. The molecule of Claim 1 wherein the site on the MN protein to which
CANCELLED said vertebrate cells adhere in said cell adhesion assay is within the proteoglycan-lik
domain or within the carbonic anhydrase domain of the MN protein.

8. The molecule of Claim 1 wherein the site on the MN protein
CANCELLED comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:
~~10 and~~ 97-106.

9. The molecule of Claim 1 wherein the site on the MN protein has an
CANCELLED amino acid sequence selected from the group consisting of SEQ ID NOS: 10 and 97-
106.

CANCELLED

10. The molecule of Claim 1 wherein said vertebrate cells are ~~mammalian~~.

CANCELLED

~~11. The molecule of Claim 1 wherein said vertebrate cells are human~~.

NOT SEARCHED/ EXAMINED

12. A MN protein or MN polypeptide which mediates attachment of vertebrate cells in a cell adhesion assay, wherein said MN protein or MN polypeptide when introduced into the extracellular fluid environment of vertebrate cells prevents the formation of intercellular contacts and the adhesion of said vertebrate cells to each other.

NOT SEARCHED/ EXAMINED

13. The MN protein or MN polypeptide of Claim 12 which when introduced into the extracellular fluid environment of a vertebrate preneoplastic or neoplastic cell that abnormally expresses MN protein, inhibits the growth of said cell.

NOT SEARCHED/ EXAMINED

14. The MN protein or MN polypeptide of Claim 12 whose amino acid sequence is from SEQ ID NO: 97, from SEQ ID NO: 50, or from SEQ ID NO: 51.

NOT SEARCHED/ EXAMINED

15. The MN protein or MN polypeptide of Claim 12 whose amino acid sequence is from SEQ ID NO: 50.

NOT SEARCHED/ EXAMINED

16. The MN protein or MN polypeptide of Claim 12 which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 10 and 97-106.

NOT SEARCHED/ EXAMINED

17. The MN polypeptide of Claim 12 that is selected from the group consisting of SEQ ID NOS: 10 and 97-106.

NOT SEARCHED/ EXAMINED

18. The MN protein or MN polypeptide of Claim 12 that is specifically bound by eith r the M75 monoclonal antibody that is secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128, or by the MN12 monoclonal antibody that is secreted from the hybridoma

MN 12.2.2, which was deposited at the American Type Culture Collection under ATCC No. HB 11647, or by both said monoclonal antibodies.

19. A method of identifying a site on an MN protein to which vertebrate cells adhere by testing a series of overlapping polypeptides from said MN protein in a cell adhesion assay with vertebrate cells, and determining that if cells adhere to a polypeptide from said series, that said polypeptide comprises a site on said MN protein to which vertebrate cells adhere.

NOT SEARCHED/ EXAMINED

20. A vector comprising an expression control sequence operatively linked to a nucleic acid encoding the variable domains of a MN-specific antibody, wherein said domains are separated by a flexible linker polypeptide, and wherein said vector, when transfected into a vertebrate preneoplastic or neoplastic cell that abnormally expresses MN protein, inhibits the growth of said cell.

NOT SEARCHED/ EXAMINED

21. The vector of Claim 20 wherein said expression control sequence comprises the MN gene promoter operatively linked to said nucleic acid.

NOT SEARCHED/ EXAMINED

22. The vector of Claim 20 wherein said flexible linker polypeptide has the amino acid sequence of SEQ ID NO: 116.

NOT SEARCHED/ EXAMINED

23. The vector of Claim 20 wherein said expression control sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NO: 21, SEQ ID NO: 27 and SEQ ID NO: 91.

NOT SEARCHED/ EXAMINED

24. A vector comprising a nucleic acid that encodes a cytotoxic protein or cytotoxic polypeptide operatively linked to the MN gene promoter, wherein said vector, when transfected into a vertebrate preneoplastic or neoplastic cell that abnormally expresses MN protein, inhibits the growth of said cell.

NOT SEARCHED/ EXAMINED

25. The vector of Claim 24 wherein said cytotoxic protein is HSV thymidine kinase.

NOT SEARCHED/ EXAMINED

26. The vector according to Claim 24 wherein said vector further comprises a nucleic acid encoding a cytokine operatively linked to said MN gene promoter.

NOT SEARCHED/ EXAMINED

27. The vector of Claim 26 wherein said cytokine is interferon or interleukin-2.

CANCELLED

~~28. A repressor complex that binds to the MN gene promoter.~~

CANCELLED

29. The repressor complex of Claim 28 that binds to SEQ ID NO: 115 of ~~the MN gene promoter.~~

CANCELLED

30. The repressor complex of Claim 29 comprising two proteins having ~~molecular weights of 35~~ and 42 kilodaltons, respectively.

31. A protein or a polypeptide that binds specifically to a site on a MN protein to which vertebrate cells adhere in a cell adhesion assay as described in Example 2, wherein said protein or polypeptide when tested in vitro inhibits the adhesion of vertebrate cells to MN protein, and wherein said protein or polypeptide comprises one or more of the heptapeptides SEQ ID NOS: 107, 108 and 109, or one or both of the nonapeptides SEQ ID NOS: 137 and 138, and wherein said protein or polypeptide is not a MN-specific antibody.

32. The polypeptide of Claim 31 selected from the group consisting of SEQ ID NOS: 107, 108, 109, 137 and 138.

33. A method of identifying an organic or an inorganic molecule that binds specifically to a site on a MN protein, to which vertebrate cells adhere in a cell adhesion assay, comprising testing organic and inorganic molecules in a cell adhesion assay as described in Example 2, and identifying molecules that inhibit the adhesion of vertebrate cells to said MN protein as specifically binding to said site.

34. The method of Claim 33 wherein said molecule is organic.

35. The method of Claim 33 wherein said molecule is inorganic.

36. The method of Claim 34 wherein said molecule is a protein or a polypeptide.

37. The method of Claim 36 wherein said protein or polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 107, 108, 109, 137 and 138.

38. The method of Claim 34 wherein said polypeptide is selected from the group consisting of SEQ ID NOS: 107, 108, 109, 137 and 138.

39. The method of Claim 33 wherein said organic or inorganic molecule, when in contact with a vertebrate preneoplastic or neoplastic cell that abnormally expresses MN protein, inhibits the growith of said cell.

40. The method of Claim 33 wherein the site on the MN protein to which said vertebrate cells adhere in said cell adhesion assay is within the proteoglycan-like domain or within the carbonic anhydrase domain of the MN protein.

41. The method of Claim 33 wherein the site on the MN protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 10 and 97-106.

42. The method of Claim 33 wherein the site on the MN protein has an amino acid sequence selected from the group consisting of SEQ ID NOS: 10 and 97-106.

43. The method of Claim 33 wherein said vertebrate cells are mammalian cells.

44. The method of Claim 33 wherein said vertebrate cells are human cells.

45. A repressor complex, comprising two proteins having molecular weights of 35 and 42 kilodaltons, respectively, that binds to SEQ ID NO: 115 of the MN gene promoter.

CANCELLED 46. The repressor complex of Claim 45 that binds to SEQ ID NO: ~~115 of the MN gene promoter~~.

47. The repressor complex of Claim 45 that binds to SEQ ID NO: 143 of the MN gene promoter.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/63, 9/88, C07R 16/40

A2

(11) International Publication Number: WO 00/24913

(43) International Publication Date: 4 May 2000 (04.05.00)

(21) International Application Number: PCT/US99/24879

(22) International Filing Date: 22 October 1999 (22.10.99)

(30) Priority Data:

09/177,776	23 October 1998 (23.10.98)	US
09/178,115	23 October 1998 (23.10.98)	US

(71) Applicant *(for AM BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG only)*: BAYER CORPORATION [US/US]; 63 North Street, Medfield, MA 02052 (US).

(71) Applicant *(for all designated States except US)*: INSTITUTE OF VIROLOGY [SK/SK]; Slovak Academy of Sciences, Dubravska Cesta 9, 842 46 Bratislava (SK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ZAVADA, Jan [CZ/CZ]; Na pekne vyhlidce 1, 160 00 Prague 6 (CZ). PASTOREKOVA, Silvia [SK/SK]; I. Bukovcana 18, 841 07 Bratislava (SK). PASTOREK, Jaromir [SK/SK]; I. Bukovcana 18, 841 07 Bratislava (SK).

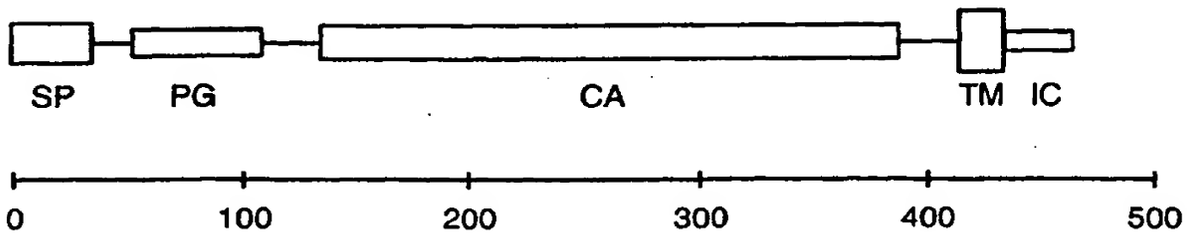
(74) Agent: LAUDER, Leona, L.; Suite 610, 369 Pine street, San Francisco, CA 94104–3313 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: MN GENE AND PROTEIN



(57) Abstract

Identified herein is the location of the MN protein binding site, and MN proteins/polypeptides that compete for attachment to vertebrate cells with immobilized MN protein. Such MN proteins/polypeptides prevent cell–cell adhesion and the formation of intercellular contacts. The MN protein binding site is a therapeutic target that can be blocked by organic or inorganic molecules, preferably organic molecules, more preferably proteins/polypeptides that specifically bind to that site. Therapeutic methods for inhibiting the growth of preneoplastic/neoplastic vertebrate cells that abnormally express MN protein are disclosed. Vectors are provided that encode the variable domains of MN–specific antibodies and a flexible linker polypeptide separating those domains. Further vectors are disclosed that encode a cytotoxic protein/polypeptide operatively linked to the MN gene promoter, and which vectors preferably further encode a cytokine. The MN gene promoter is characterized, and the binding site for a repressor of MN transcription is disclosed.

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
D-0021.5 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/24879	22/10/1999	23/10/1998
Applicant		
BAYER CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 8

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/24879

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C12N 9/88, C07K 16/40 | A3

(11) International Publication Number: WO 00/24913

(43) International Publication Date: 4 May 2000 (04.05.00)

(21) International Application Number: PCT/US99/24879

(22) International Filing Date: 22 October 1999 (22.10.99)

(30) Priority Data:

09/177,776	23 October 1998 (23.10.98)	US
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(71) Applicant *(for AM BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG only)*: BAYER CORPORATION [US/US]; 63 North Street, Medfield, MA 02052 (US).

(71) Applicant *(for all designated States except US)*: INSTITUTE OF VIROLOGY [SK/SK]; Slovak Academy of Sciences, Dubravska Cesta 9, 842 46 Bratislava (SK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ZAVADA, Jan [CZ/CZ]; Na pekne vyhlidce 1, 160 00 Prague 6 (CZ). PASTOREKOVA, Silvia [SK/SK]; I. Bukovcana 18, 841 07 Bratislava (SK). PASTOREK, Jaromir [SK/SK]; I. Bukovcana 18, 841 07 Bratislava (SK).

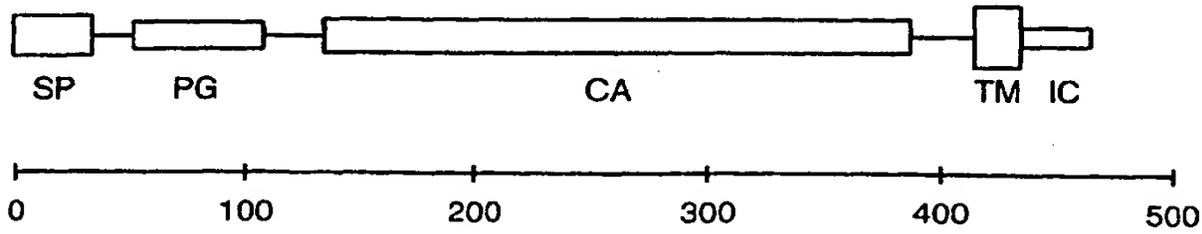
(74) Agent: LAUDER, Leona, L.; Suite 610, 369 Pine street, San Francisco, CA 94104-3313 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
14 September 2000 (14.09.00)

(54) Title: MN GENE AND PROTEIN



(57) Abstract

Identified herein is the location of the MN protein binding site, and MN proteins/polypeptides that compete for attachment to vertebrate cells with immobilized MN protein. Such MN proteins/polypeptides prevent cell–cell adhesion and the formation of intercellular contacts. The MN protein binding site is a therapeutic target that can be blocked by organic or inorganic molecules, preferably organic molecules, more preferably proteins/polypeptides that specifically bind to that site. Therapeutic methods for inhibiting the growth of preneoplastic/neoplastic vertebrate cells that abnormally express MN protein are disclosed. Vectors are provided that encode the variable domains of MN–specific antibodies and a flexible linker polypeptide separating those domains. Further vectors are disclosed that encode a cytotoxic protein/polypeptide operatively linked to the MN gene promoter, and which vectors preferably further encode a cytokine. The MN gene promoter is characterized, and the binding site for a repressor of MN transcription is disclosed.

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INTERNATI L SEARCH REPORT

Interr. /Application No
PCT/US 99/24879

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N9/88 C07K16/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZAVADA, J. ET AL.: "Transient transformation of mammalian cells by MN protein, a tumor-associated cell adhesion molecule with carbonic anhydrase activity" INTERNATIONAL JOURNAL OF ONCOLOGY, vol. 10, no. 4, April 1997 (1997-04), pages 857-863, XP000909801 the whole document	1-4, 10-19
X	WO 95 34650 A (CIBA CORNING DIAGNOSTICS CORP ;INST OF VIROLOGY (SK); ZAVADA JAN () 21 December 1995 (1995-12-21) cited in the application page 3, line 4 -page 5, line 37; figure 1 page 56, line 6 -page 61, line 16 page 29, line 17 -page 30, line 30 page 44, line 30 -page 46, line 2	12-29
A	examples 1,4	1-11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 2000	23.06.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kaas, V

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/24879

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9534650 A	21-12-1995	US 5981711 A	09-11-1999
		US 5955075 A	21-09-1999
		US 5989838 A	23-11-1999
		AU 2861695 A	05-01-1996
		CA 2192678 A	21-12-1995
		EP 0763110 A	19-03-1997
		US 5972353 A	26-10-1999
		US 6027887 A	22-02-2000

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	OPAVSKY, R.: "Human MN/CA9 gene, a novel member of carbonic anhydrase family: structure and exon to protein domain relationships" GENOMICS, vol. 33, no. 3, 1 May 1996 (1996-05-01), pages 480-487, XP000909773	12-19, 24-27
A	the whole document	1-11
X	PASTOREK ET AL: "Cloning and characterization of MN, a human tumor-associated protein with a domain homologous to carbonic anhydrase and a putative helix-loop-helix DNA binding segment" ONCOGENE,GB,BASINGSTOKE, HANTS, vol. 9, no. 10, October 1994 (1994-10), pages 2877-2888, XP002131890 ISSN: 0950-9232	12-19
A	the whole document	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/24879

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 and 28 relate to a compound/complex defined by reference to a desirable characteristic or property, namely the ability to specifically bind to a site on the MN protein and the ability to inhibit the adhesion of cells to MN protein (claim 1) and the ability to bind and repress the MN gene promoter.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method/apparatus by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, as regards claim 1, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the heptapeptides prepared in example 3 on pages 70-71. Given that the application fails to identify any "repressor complex", the search concerning claim 28 has been restricted to antisense constructs as defined on pages 38-39 of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-11

An organic or inorganic molecule that binds specifically to a site on a MN protein and inhibits the adhesion of cells to the MN protein in vitro.

2. Claims: 12-19

A MN protein or MN polypeptide which prevents the formation of intracellular contacts and the adhesion of vertebrate cells to each other.

3. Claims: 20-23

A vector comprising a nucleic acid encoding the variable domains of a MN-specific antibody wherein said domains are separated by a flexible linker polypeptide.

4. Claims: 24-27

A vector comprising a nucleic acid that encodes a cytotoxic protein operably linked to a MN gene promoter.

5. Claims: 28-30

A repressor complex that binds to the MN gene promoter.